AFRL-AFOSR-VA-TR-2015-0260

Self-Powered Optical Spectroscopy

Audrey Elerbee
LELAND STANFORD JUNIOR UNIV CA

08/27/2015
Final Report

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*
05/19/2015

2. REPORT TYPE
Final Report

3. DATES COVERED *(From - To)*
MAY 2012-MAY 2015

4. TITLE AND SUBTITLE
Self-Powered Optical Spectroscopy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
FA9550-12-1-0269

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Audrey Ellerbee

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Board of Trustees of the Leland Stanford Junior University
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
USAF, AFRL DUNS 143574726
AF Office of Scientific Research
875 North Randolph Street, RM 3112
Arlington, VA 22203

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
A. Approved for public release

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Main goal: to develop new techniques for low-cost optical spectroscopy that enable quantitative measurements in poor-resource environments. The realized techniques span a broad optical range: UV through near infrared. Major technologies developed include: 1) a new low-cost, nanoparticle-based strategy for non-invasive measurement of whole sample bodily fluids; 2) a new platform for robust colorimetric assay for measurement for point-of-care health monitoring; 3) a new technique for low-cost polarization spectroscopy in the infrared for molecular contrast imaging of biological tissue. Outcomes: 2 peer-reviewed publications, 1 more in preparation, 1 archival conference paper, and 2 invention disclosures.

15. SUBJECT TERMS
spectroscopy, nanoparticles, medical diagnostics, point-of-care, polarization, microscopy

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON / 19b. TELEPHONE NUMBER *(Include area code)*
U	U	U	SAR	7	Audrey Ellerbee, PI / 650-725-4842

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Audrey K Ellerbee
Final Report
Self-powered optical spectroscopy

Executive Summary. Quantitative optical spectroscopy is a powerful technique for analyzing the chemical composition of many materials: the interaction of optical photons with the underlying chemical bonds in materials produces a unique optical signature for molecular fingerprinting or resolving physical structures. In many ways, absorption and transmission spectroscopy are fundamentally connected to the ways our eyes perceive the beautiful colors that enrich how humans view the world; moreover, spectroscopy in the UV and infrared regimes – although outside the bandwidth of the human perceptual system – still plays an important role in many measurement systems. With the onset of globalization, however, has come a recognition that not all measurement environments are equally resourced. Hence, as the technology germane to optical spectroscopy improves – yielding smaller, cheaper, more powerful light sources and faster, more efficient and effective detectors with smaller footprints – there remains an ongoing need to incorporate such enabling ideas and components into new strategies for better measurement systems that are more robust to large variations and consistency in available resources – be they electrical, financial or intellectual.

This project aimed to propose and prototype new techniques for quantitative optical spectroscopy that specifically consider methods to achieve high performance in the face of fewer resources. The outcome of this work has yielded three new technologies – each aimed to exploit photons in a different wavelength regime (UV, visible or infrared) for the purpose of optical spectroscopy – in order to understand and interpret the interaction of light with biological samples.

In the first aim, with a goal of enabling UV spectroscopy using visible light detectors, we developed a new strategy in which the natural photoluminescence of quantum dots is used as an optical transducer to passively convert UV radiation into a visible wavelength signal – a form of reverse upconversion, or "downconversion." We showed that when extruded into large-area films, these nanoparticle-based substrates were efficient and sufficient to enable quantitative measurement of the concentration of undiluted body fluids such as urine and whole blood. Our QD-based sensor is the first instrument capable of non-contact measurement of the concentration of analytes (specifically, glucose) in unprepped biological samples whose 3.5-μM limit of detection rivals the best demonstrated alternative strategies while simultaneously having a dynamic range that spans the entire clinically relevant range for the analytes of interest. In addition, we showed that integration of a cell phone detector yielded a system with similar performance to its expensive research grade counterpart instrument, a standard spectrophotometer.

In the second aim, with the goal of making robust, quantitative measurements of colorimetric dipstick assays at visible wavelengths, we developed a new platform for sample loading and sample delivery that is amenable to point-of-care applications when operated by unskilled users. While the work for this aim is ongoing, we have already

demonstrated that the general strategy we pursue can address for major barriers to acceptance of this ubiquitous technology as a definitive diagnostic tool in the hands of ordinary persons and provides new opportunities for at-home monitoring that broaden access to reliable healthcare.

In the third aim, with the goal of facilitating polarization-sensitive detection using near-infrared spectroscopy, we demonstrate a new strategy for near-infrared spectroscopic interferometry (based on optical coherence tomography) to expedite the process of polarization-sensitive detection of biological tissue (i.e. identify birefringence). Our design for a passive optical structure to enable interleaved optical frequency combs comprising orthogonal polarization states can be used to replace other active, more expensive polarization components and contribute to faster measurements overall, realizing gains in system performance in the face of lower financial resources. Our proof-of-principle demonstrations of the concept using calibrated polarizing components and biological tissue reveal that this strategy represents a new platform for faster, depth-selective imaging while providing label-free molecular contrast.

A brief summary of the main results for this work follows; the reader is encouraged to review our peer-reviewed publications for more details.

AIM 1: Fabricate large-area nanoparticle films for low-cost UV spectroscopy

Abstract: We present a label-free, optical sensor for biomedical applications based on changes in the visible photoluminescence (PL) of quantum dots in a thin polymer film. Using glucose as the target molecule, the screening of UV excitation due to pre-absorption by the product of an enzymatic assay leads to quenching of the PL of quantum dots (QDs) in a non-contact scheme. The irradiance changes in QD PL indicate quantitatively the level of glucose present. The non-contact nature of the assay prevents surface degradation of the QDs, which yields an efficient, waste-free, cost-effective, portable, and sustainable biosensor with attractive market features. The limit of detection of the demonstrated biosensor is ~3.5 μm, which is competitive with existing contact-based bioassays. In addition, the biosensor operates over the entire clinically relevant range of glucose concentrations of biological fluids including urine and whole blood. The comparable results achieved across a range of cost-affordable detectors, including a spectrophotometer, portable spectrometer, and iPhone camera, suggest that label-free and visible quantification of glucose with QD films can be applied to low-cost, point-of-care biomedical sensing as well as scientific applications in the laboratory for characterizing glucose or other analytes.

Results Highlight

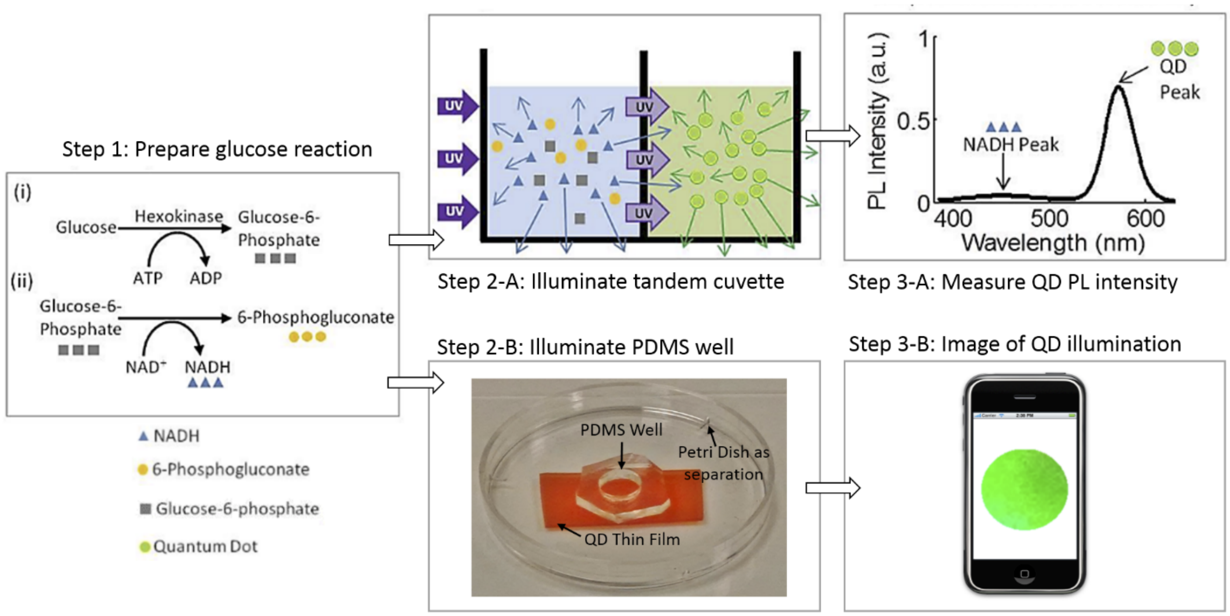

Figure 1-Illustration of Technique. Schematic illustration of a non-contact optical transduction for the quantitation of glucose with either colloidal quantum dots in a tandum cuvette (route A) or quantum dot thin films (route B). The fluorescent by-product (NADH) of a hexokinase-glucose 6-phosphate dehydrogenase enzymatic glucose assay absorbs UV excitation light, leading to increased NADH fluorescence and reduced QD PL compared to when no glucose is present. The concentration of glucose present is a direct function of the QD PL, which occurs in the visible range. Residual NADH PL does not interfere with the measurement.

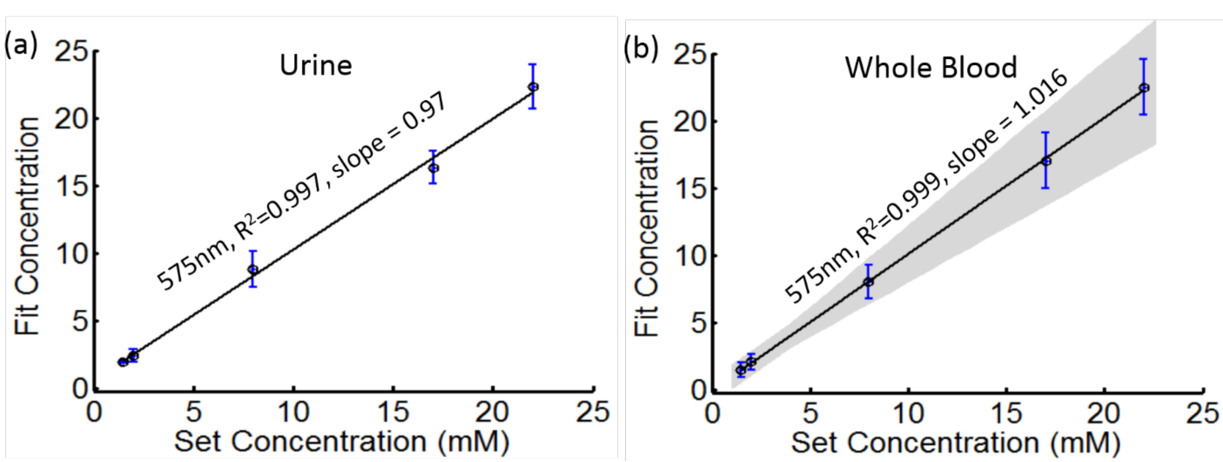

Figure 2-Sample accuracy for biological fluids. Set vs Fit graphs for (a) urine and (b) whole blood. Shaded region in (b) represents the accepted ISO standards for blood glucose meters. Data points correspond to mean ± standard deviation (n = 6).

Research Outcomes

1. Invention disclosure filed
2. Khan, S.A., Smith, G.T., Seo, F. and **A.K. Ellerbee,** "Label-free and noncontact optical biosensing of glucose with quantum dots," Biosensors and Bioelectronics, 64, 30-35 (2014): DOI: 10.1016/j.bios.2014.08.035
3. Khan, S.A., Smith, G.T. and A.K. Ellerbee, "Label-free assay for the detection of glucose mediated by the effects of narrowband absorption on quantum dot photoluminescence," Oral Presentation, San Francisco, Proc. SPIE 89330A1-7 (2014).

AIM 2: Implement a new strategy for low-cost, volume- and timing-controlled point-of-care sample delivery for accurate visible light spectroscopy

Abstract: We designed and fabricated a device that allows for robust and quantitative colorimetric measurements of dipstick assays, specifically for urinalysis. The high rate of user error associated with using and reading the results of dipstick assays has rendered them unreliable in the hands of unsilled users, outside of a clinical setting. We aim to remove the user error associated with properly preparing the dipstick, therefore, making them amenable for at-home monitoring in low-resource settings. We modified the original nano-liter volume SlipChip device to create a low-cost sample delivery system capable of accurately transferring microliter volumes. We then couple the chip with a unique light-shielding box to control lighting conditions and mate the system with a standard cell phone camera for quantitative readout. We show that transferring an accurate volume to dipstick assays is a crucial factor in the accuracy of visible light spectroscopy for accurate measurement of analyte concentration. Our device can be easily altered to transfer differing volumes, allowing it to be used for dipstick assays beyond those for urinalysis. Efforts in removing other sources of user error (e.g., reading the results of the assays at the correct time) and a comprehensive validation of the device are ongoing.

Results Highlight

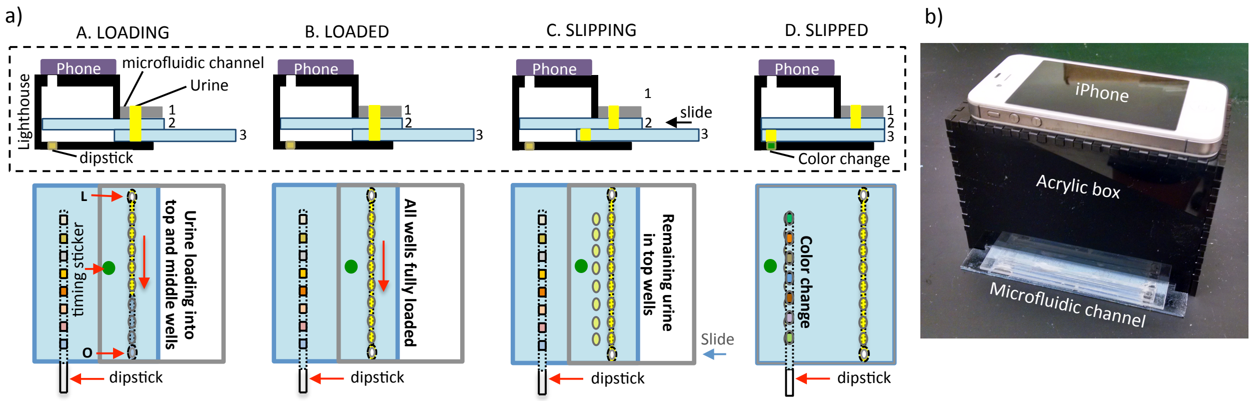

Figure 1 – System schematic. a) Illustration of operating principle of urinalysis device. The size of wells in slide 3 dictates the volume transferred to the dipstick assay. L: loading, O: outlet. b) Image of actual device after slipping of slide 3.

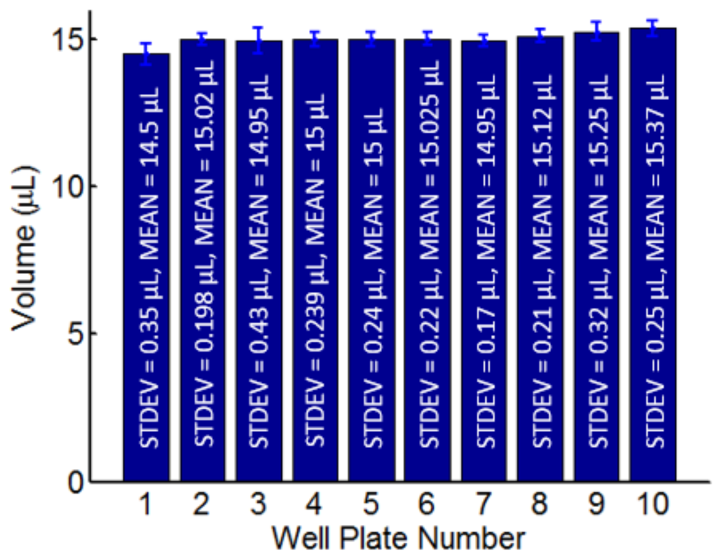

Figure 2 – Volume Control Results. Dipstick well plate number loaded with fluid according to system schematic and measurement of fluid after device is slipped. N = 7 trials were conducted for validation of the device. Results speak to the accuracy of the device for delivery of correct sample volumes.

<u>Research Outcomes</u>

1. Invention disclosure filed.
2. Peer-reviewed manuscript in preparation.

AIM 3: Implement a new strategy for low-cost, depth-resolved, near-infrared polarization spectroscopy

Abstract: We introduce a new strategy for single-mode fiber based polarization-sensitive (PS-) optical coherence tomography (OCT) using orthogonally polarized optical frequency combs (OFC) in the sample arm. The two OFCs are tuned be interleaved in the spectral domain, permitting simultaneous measurement of both polarization states from the same spatial region, close to the location of zero pathlength delay. The two polarization states of the beam in the sample arm are demultiplexed by interpolation after performing wavelength stabilization via a two-mirror calibration method. A particularly attractive aspect of this measurement technique is the ability to reduce the number of detectors used to sample the data, yielding a cost savings for the system overall. The system uses Jones matrix methods to measure quantitatively the round-trip phase retardation B-scans in the sample. A glass plate and quarter-wave plate were measured to validate the accuracy of the birefringence measurement. Further, we demonstrated the potential of this system for biomedical applications by measurement of chicken breast muscle.

Results Highlight

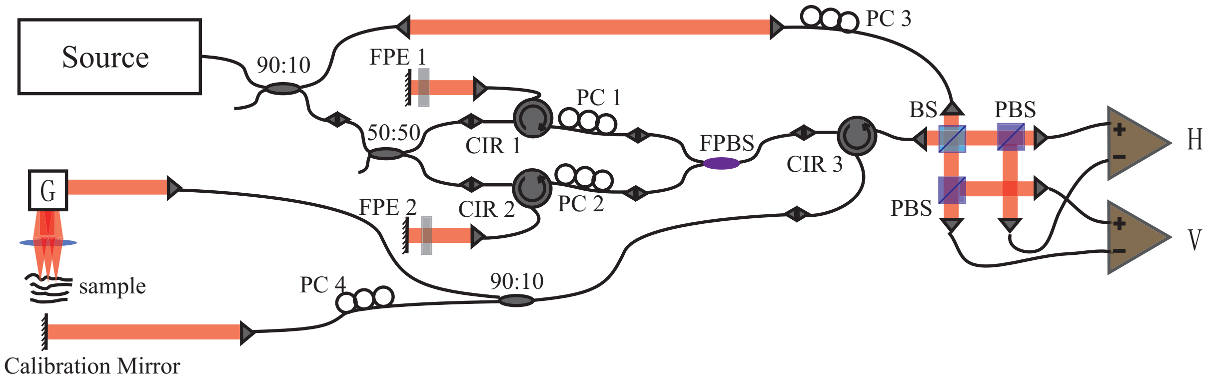

Fig. 1. Schematic of the PS-iOCT system with orthogonally polarized optical frequency
combs. FPE: Fabry-Perot etalon; PC: polarization controller; FPBS, fiber polarizing beam splitter; CIR: circulator; BS: non-polarizing beam splitter; PBS: polarizing beam splitter; G, galvanometers.

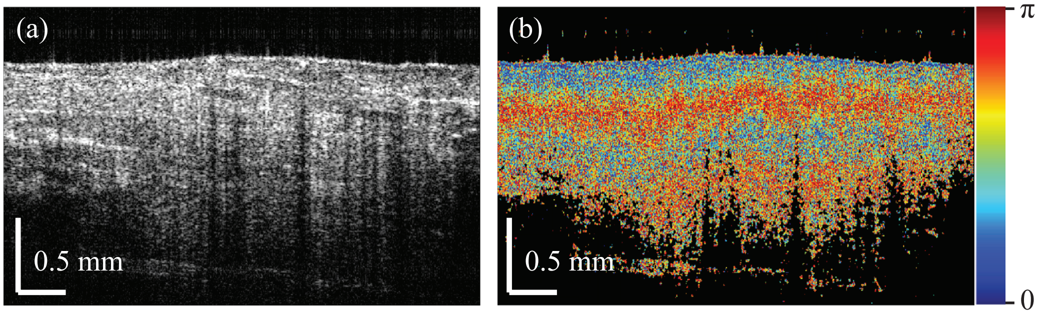

Fig. 2. Intensity (a) and retardation (b) PS-OCT images of ex vivo chicken breast. The additional contrast shown by the banded structure of the chicken breast image speaks to the aligned collagen in the tissue that is not perceptible in the intensity image alone.

<u>Research Outcomes</u>

1. Duan, L., Marvdashti, T, **A.K. Ellerbee,** "Polarization-sensitive interleaved optical coherence tomography," *Optics Express* 23(10) 13693-13703 (2015)

1.

1. Report Type

Final Report

Primary Contact E-mail
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650-725-4842

Organization / Institution name

Stanford University

Grant/Contract Title
The full title of the funded effort.

Self-powered optical spectroscopy

Grant/Contract Number
AFOSR assigned control number. It must begin with "FA9550" or "F49620" or "FA2386".

FA9550-12-1-0269

Principal Investigator Name
The full name of the principal investigator on the grant or contract.

Audrey Ellerbee

Program Manager
The AFOSR Program Manager currently assigned to the award

John Luginsland

Reporting Period Start Date

05/15/2012

Reporting Period End Date

05/14/2015

Abstract

The main goal of this project was to develop new techniques for low-cost optical spectroscopy that enable quantitative measurements in situations and environments that may lack resources germane to existing techniques. The realization of such techniques throughout the course of the project has come in various forms. Firstly, we developed a novel strategy for absorption spectroscopy on the basis of quenching of quantum dot photoluminescence. This work was demonstrated as a potential technique for non-invasive measurement of blood glucose and was demonstrated in whole blood and urine samples. The outcome of this work was published in a peer-reviewed journal and presented in oral form at a research conference. We also filed an invention disclosure with our school’s office of technology licensing, but recently decided not to pursue patenting it.

1. Khan, S.A., Smith, G.T., Seo, F. and A.K. Ellerbee, "Label-free and noncontact optical biosensing of glucose with quantum dots," Biosensors and Bioelectronics, 64, 30-35 (2014): DOI: 10.1016/j.bios.2014.08.035

2. Khan, S.A., Smith, G.T. and A.K. Ellerbee, “Label-free assay for the detection of glucose mediated by the effects of narrowband absorption on quantum dot photoluminescence,” Oral Presentation, San Francisco,

Proc. SPIE 89330A1-7 (2014).

Secondly, we have been working to develop a novel strategy for robust visible-wavelength spectroscopic measurements of colorimetric dipstick assays. This work would be particularly useful for enabling at-home spectral analysis of bodily fluids like urine to facilitate testing for disease. The work for this project is ongoing; we expect to submit a peer-reviewed journal publication on it later this calendar year and have filed an invention disclosure with our school's office of technology licensing.

Thirdly, we introduced a novel strategy for a depth-resolved polarization spectroscopy measurement in the infrared regime based on spectral interleaving and optical coherence tomography. This work allows quantitative measurements of birefringence in biological samples using a low-cost, passive optical device as an alternative to use of more expensive electro-optic modulators. The outcome of this work was published in a peer-reviewed journal.

3. Duan, L., Marvdashti, T, A.K. Ellerbee, "Polarization-sensitive interleaved optical coherence tomography," Optics Express 23(10) 13693-13703 (2015)

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Archival Publications (published) during reporting period:

Khan, S.A., Smith, G.T., Seo, F. and A.K. Ellerbee, "Label-free and noncontact optical biosensing of glucose with quantum dots," Biosensors and Bioelectronics, 64, 30-35 (2014): DOI: 10.1016/j.bios.2014.08.035

Khan, S.A., Smith, G.T. and A.K. Ellerbee, "Label-free assay for the detection of glucose mediated by the effects of narrowband absorption on quantum dot photoluminescence," Oral Presentation, San Francisco, Proc. SPIE 89330A1-7 (2014).

Duan, L., Marvdashti, T, A.K. Ellerbee, "Polarization-sensitive interleaved optical coherence tomography," Optics Express 23(10) 13693-13703 (2015)

Changes in research objectives (if any):

The proposal included two specific aims, which we will consider as the objectives:

Aim 1 – Fabricate microparticles with controlled spectral and intensity profiles
Aim 2 - Large-area control and arrangement of collections of nanoparticles

Experiments to complete the original Aim 1 were carried out, but the rapidly changing technology landscape made the proposed strategy less relevant and impactful than intended as the research progressed; hence, we embraced the emerging technology trends (e.g., use of mobile phone cameras as cheap, portable devices for quantitative measurements) and carried out a modified selection of projects

that yielded alternative outcomes of greater significance.

Aim 1 (revised) – Fabricate large-area nanoparticle films for low-cost UV spectroscopy
Aim 2 (revised) – Implement a new strategy for low-cost, volume- and timing-controlled point-of-care sample delivery for accurate visible light spectroscopy
Aim 3 (revised) – Implement a new strategy for low-cost, depth-resolved, near-infrared polarization spectroscopy

Change in AFOSR Program Manager, if any:

Original program manager, Howard Schlossberg, retired during the reporting period, and was replaced by the new program manager, John Luginsland

Extensions granted or milestones slipped, if any:

No milestones were set forth in the original proposal.

AFOSR LRIR Number

LRIR Title

Reporting Period

Laboratory Task Manager

Program Officer

Research Objectives

Technical Summary

Funding Summary by Cost Category (by FY, $K)

	Starting FY	FY+1	FY+2
Salary			
Equipment/Facilities			
Supplies			
Total			

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Report Document - Text Analysis

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Appendix Documents

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